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Copper-mediated asymmetric transformations*

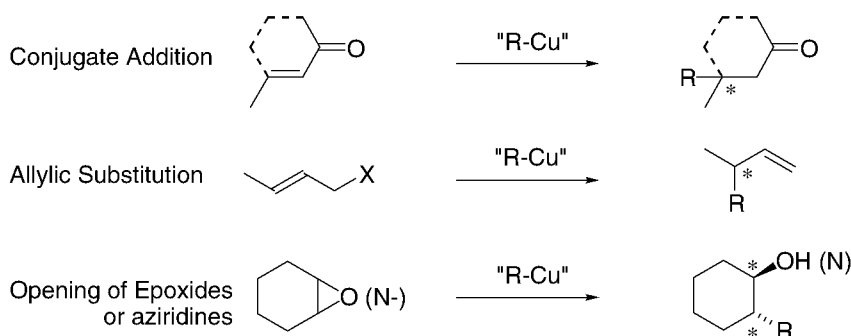
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Abstract: Copper-catalyzed reactions include the enantioselective conjugate addition and the S_N2' substitution. We describe the genesis of these reactions, the choice of the primary organometallic reagent, and our studies on finding new Michael acceptors and new ligands. We also report on the use of the zinc enolate generated upon conjugate addition.

INTRODUCTION

Organocopper chemistry has found widespread synthetic uses [1]. Several of the reactions promoted by Cu salts generate new stereogenic centers, and efforts have been directed toward the control of the absolute stereochemistry [2]. The main reactions are the conjugate addition, the S_N2' substitution and the opening of *meso* epoxides or aziridines (Scheme 1).



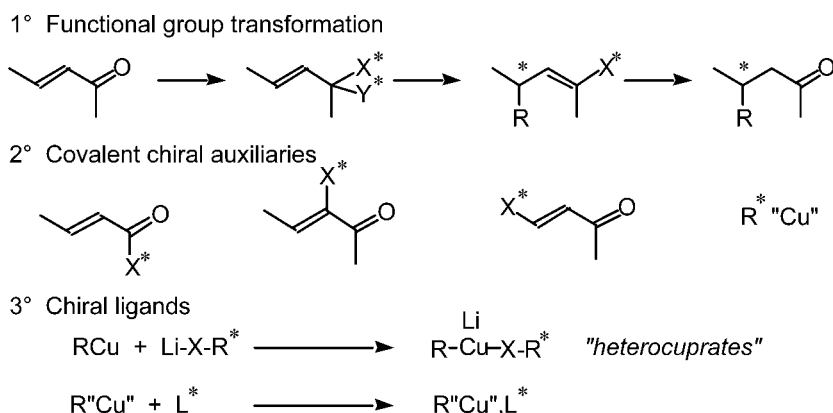
Scheme 1 Main asymmetric organocopper transformations

Our work dealt with all three reactions with a strong emphasis on the conjugate addition, the most studied one.

CONJUGATE ADDITION

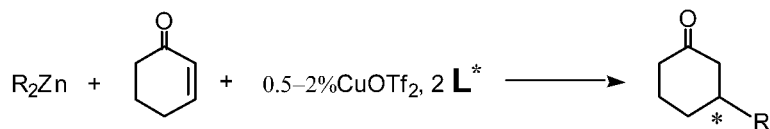
There are several ways to undergo an asymmetric conjugate addition reaction. They are summarized in Scheme 2. Among them, only the use of chiral ligands allows for a catalytic version, the most desired one.

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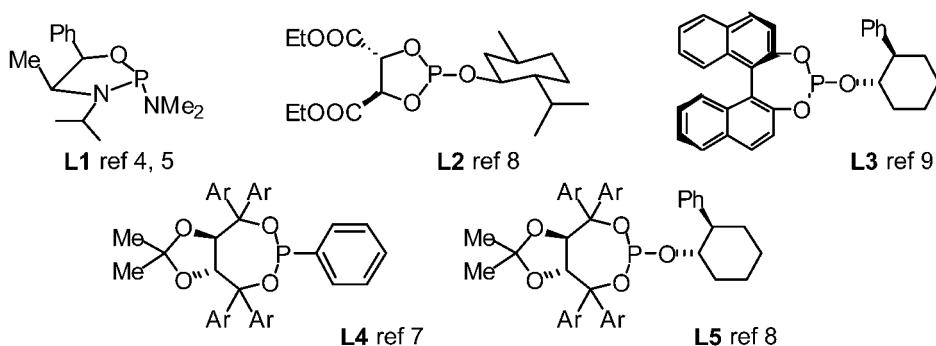
Scheme 2 Ways for enantioselective conjugate addition.

In the catalytic conjugate addition, a primary organometallic reagent has to transmetallate to a copper reagent, which, itself, undergoes the reaction [3]. Until 1993, all authors have relied upon the use of Grignard reagents, whereupon we introduced the idea of using diorganozinc reagents instead [4]. The needed chiral information was brought by a trivalent phosphorus ligand, a type of chiral ligand we also introduced in organocopper chemistry, in 1991 [5]. This combination of reagents has, since then, found a widespread use (Scheme 3).



Scheme 3 Catalytic asymmetric conjugate addition.

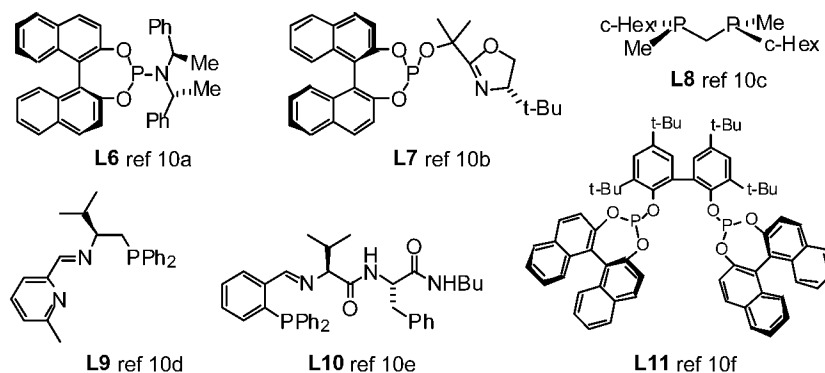
Among the various copper salts, it was found that $\text{Cu}(\text{OTf})_2$ was the most convenient, although the catalytic species should be a Cu(I) complex. A strong acceleration of the reaction is provided by the trivalent phosphorus ligand. As little as 0.5% of copper salt and 1% of ligand were needed for a quantitative yield [6] of adduct with enantioselectivities up to 98%. The solvent should be of low polarity and low Lewis basicity: Toluene, dichloromethane, and diethyl ether are appropriate, whereas THF and acetonitrile are not.



Scheme 4 Chiral trivalent phosphorus ligand used in our group.

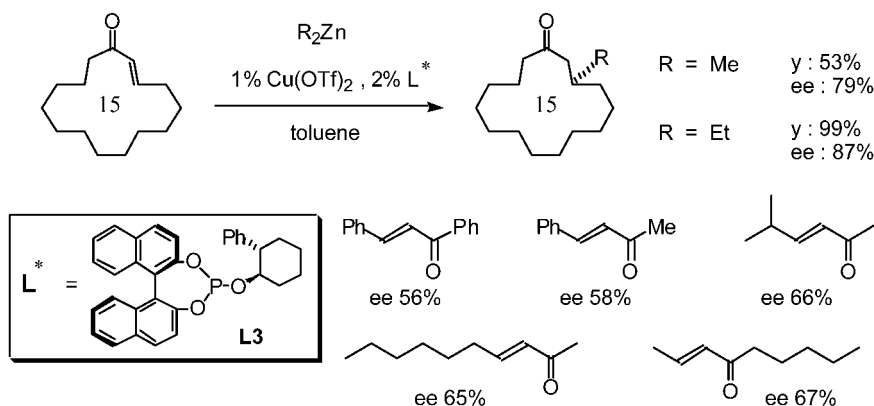
Having set the experimental conditions, it was crucial to find efficient trivalent phosphorus ligands for the highest enantiomeric excess of the conjugate adduct. Several classes of ligands were designed, most of them being of modular type, with the phosphorus atom included in a ring and an exocyclic substituent. Both the carbon framework of the ring and exocyclic substituent may be chiral, thus introducing a matched or mismatched pair of diastereomers [7]. Some of the ligands disclosed in our laboratories are shown in Scheme 4. It should be pointed out that each of them is most appropriate for a given class of Michael acceptor and that an optimum and general ligand has not yet been found.

With cyclohexenone as substrate, **L1**, based on ephedrine, gave excellent results (ee >95%) in the stoichiometric conjugate addition with lithium dialkylcuprates [4]. However, our best result, in the catalytic version was obtained with **L5**, based on TADDOL, using diethylzinc, 0.5% Cu(OTf)₂ and 1% ligand (ee 96%) [7]. Several other ligands, disclosed in the literature, afford very high enantioselectivities (up to >98%) on this substrate, the most extensively studied in the literature (Scheme 5) [10].



Scheme 5 Other chiral trivalent phosphorus ligand.

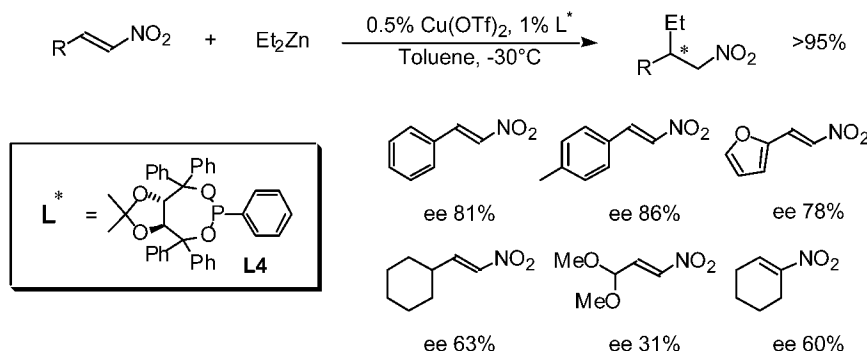
In contrast to cyclohexenone, there has been little interest on other type of enones, particularly on acyclic enones. These more challenging substrates may exist in *s-cis* or *s-trans* conformation. We have studied several acyclic enones, including a macrocyclic one, and tested many ligands (Scheme 6). It appears that **L3** gives the highest ee (79%) for the synthesis of the well-known fragrance R-(–)-Muscone. The other acyclic enone tested afford moderate to good enantioselectivities with **L3** [9].



Scheme 6 Enantioselective conjugate addition to acyclic enones.

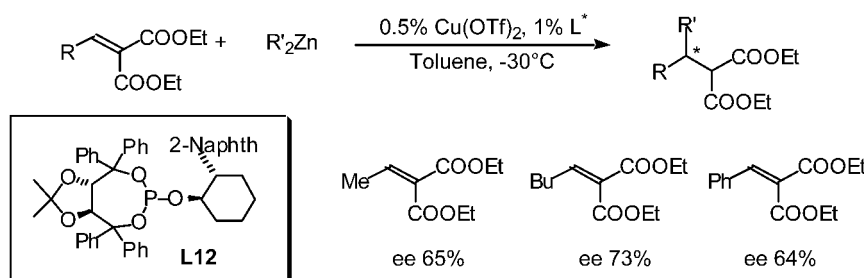
OTHER MICHAEL ACCEPTORS

During our preliminary studies on the copper-catalyzed conjugate addition of dialkyl zinc to other Michael acceptors [6], we found that nitro-olefins and alkylidene malonates were excellent substrates. Besides being the most efficient way to add alkyl groups to these substrates, the method provides ground to perform it in enantioselective fashion. We therefore tested several of our chiral ligands. In the case of nitro-olefins, the best ligand was **L4**, which afforded the highest reported enantioselectivities for most of the substrates shown in Scheme 7 [11].



Scheme 7 Enantioselective conjugate addition to nitro-olefins.

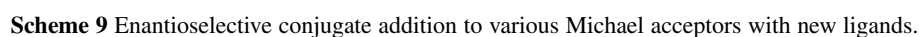
In the case of alkylidene and arylidene malonates, it was again a new ligand **L12** which afforded the highest enantioselectivities (Scheme 8) [12].



Scheme 8 Enantioselective conjugate addition to alkylidene and arylidene malonates.

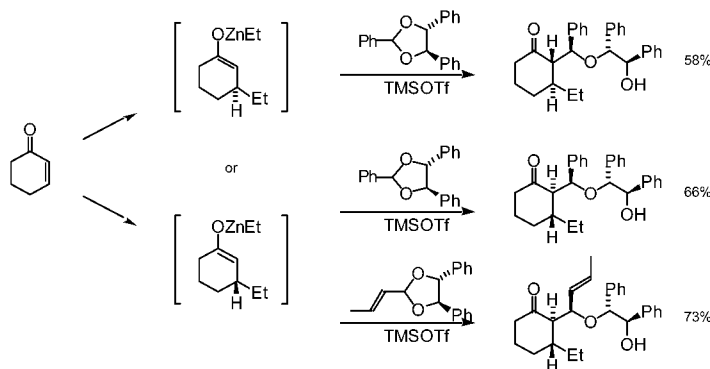
NEW BIPHENOL LIGANDS

Many of the ligands described in the literature are of modular type [10], and among them several ones rely on the atropoisomerism of the binaphthol skeleton. In search of new phosphorus ligands, we wondered if an extracyclic chiral substituent may induce a favorable atropoisomerism on a simpler biphenol skeleton. DFT calculations have shown that a rapid equilibrium would allow the matched combination to provide the required higher ligand-accelerated catalysis. Toward this end, we synthesized, among others, ligands **L13**, **L14**, and **15** by analogy to ligand **L6** (Scheme 9). Ligands **L14** and **L15** differ from **L13** by additional substitution either on the biphenol skeleton or on the chiral exocyclic amine [13].



As can be seen on selected examples (Scheme 9), these new ligands match, or even surpass, the enantioselectivity provided by the parent ligand **L6**.

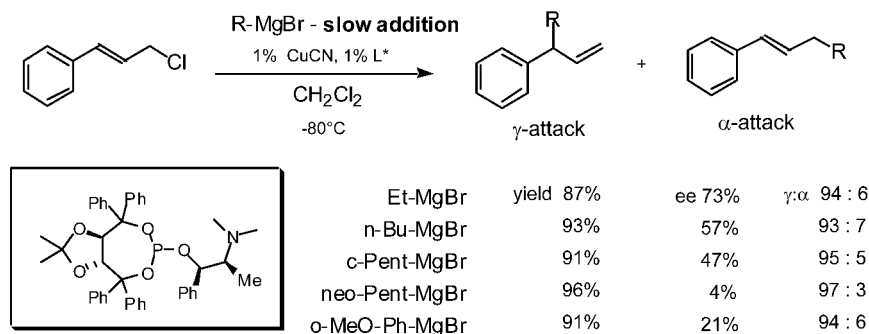
All the above conjugate additions end up with a zinc enolate, which may be trapped with other electrophiles than simple water. The reaction with aldehydes, and the Pd-catalyzed allylation, were already described by Noyori [14]. Ketones do not react. However, we found that the reaction of acetals, ketals and even orthoesters was promoted by Lewis acids, such as $\text{BF}_3 \cdot \text{OEt}_2$ or TMSOTf. Moreover, the use of chiral acetals allows for a completely stereocontrolled aldol condensation providing, at will, the *syn* or *anti* diastereomer. This control is fully exerted by the chirality of the acetal moiety (Scheme 10) [15].



Scheme 10 Trapping of zinc enolates by acetals.

The asymmetric allylic substitution has been mainly studied with Pd-based catalysts, and meso-type substrates. However, the control of the regioselectivity to the γ -position is best achieved with Cu-based catalysts. Our work on the enantioselective version of this reaction has focused on the use of Grignard reagents instead of zinc reagents. Screening of the various parameters of the reaction allowed us to find

suitable conditions for high γ selectivity, with the lowest catalyst and ligand loading (1% CuCN and 1% chiral ligands). Among the many ligands tested for this reaction, with cinnamyl chloride as model substrate, bidentate P,N ligands were found the most efficient. Representative examples are shown in Scheme 11 [16].



Scheme 11 Enantioselective γ -allylic substitution.

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